1973

PROBLEMS OF GENETIC HANDICAP

Programs of the Department of Genetics

Reliable figures on the role of genetic factors as causes of human disease and handicap are hard to document. However, one can make a reasonable case that 25% of our social load of disease, handicap and premature death can be attributed to genetic factors. The simple, clear-cut genetic diseases on which we now have definite information are only the tip of the iceberg, making up about a 10th of the genetic health problem. Far more problems present a complex mixture of genetic and environmental causes poorly understood at present -- diseases like schizophrenia, diabetes and coronary atherosclerosis. Many forms of mental retardation of learning disorders and of defects of hearing and vision also have a genetic component. Some forms of cancer, allergies, susceptibility to infection also are partly heritable. Genetic handicap is, of course, a social responsibility because of the public costs involved in caring for institutionalized children, and the general loss to the community from the human failures that may result from these handicaps. Far more important, these are poignant human problems resulting in much anguish not only to the patient, but in many cases even more to his parents and other members of the family. Besides the heavy burden involved in their sympathy with the affliction for the handicapped, and the responsibility for their care, they face also the anxiety of the possibility that lightning may strike again. We are very much concerned at Stanford with developing basic scientific knowledge that may be relevant to these problems and furthering its early application in a way that will be of obvious human benefit.

In a flash of enthusiasm about new genetic science about 50 years ago, many people advocated eugenic programs intended to prevent the spread of genetic disease. Today we have learned enough to be more humble about our ignorance, and we understand that most such programs are based on too flimsy

a foundation of scientific knowledge. When the genetics of a disease is well understood, we can of course advise prospective parents about the risks that they may face in having more children, but to tell a couple that they have a good chance of not having healthy normal children in future is hardly to be regarded as a satisfying solution to their personal problem. Furthermore, most handicapped children are born to perfectly normal parents who are unsuspecting carriers of the genetic factors that will appear in their offspring.

Research on genetic disease then focusses on two broad issues: 1) more accurate prediction of the possibility that a couple will transmit genetic defect, and 2) developing better means for preventing the birth of seriously damaged children, or of providing at least partial cures for their troubles once they are born and recognized. We will not be able to achieve those objectives without an ever deeper understanding of the way in which genes work, and the specific application of that knowledge to actual problems of genetic disease in man.

Many of the programs of the Department of Genetics are closely directed towards these goals. There is, of course, considerable additional technical information that could be communicated about them, which we would be happy to furnish, especially in response to an indication of interest in some particular area. Three long-range research projects, under the immediate direction of Dr. Joshua Lederberg, Joseph D. Grant Professor of Genetics, will be mentioned here.

For many years we have been concerned with the most basic aspects of the biochemical mechanisms by which the genes reproduce themselves in the cell, are transmitted from one cell generation to another, and then eventually determine the manner in which the cell develops. By working with microorganisms, like bacteria and viruses for these basic studies, we have been able to make great strides rather quickly and less expensively by a factor of 100 or 1000, than would be possible with work on larger and more advanced organisms. However,

when significant advances are made in the biochemistry of genes of bacteria and the major outlines worked out, these can then be applied often with remarkable fidelity to the genetics of more complex and experimentally more difficult organisms.

The current frontier of our research in bacterial gene-biochemistry is the development of methods for joining pieces of DNA molecules together end-to-end and reinserting them back into the bacterial cell. This result has been a primary experimental objective for the last 6 years and it is only within the past few months that we appear to be close to an authentic conclusion. The evidence is not yet complete but we are, in fact, investigating several promising leads simultaneously all of which appear to be working according to present evidence. The significance of this apparently arcane observation is that it now becomes possible to introduce either synthetic DNA molecules, as a kind of artificial gene, into the bacterial cell or to import pieces of genetic material from the cells of higher organisms and implant them into the bacterium. This is in no sense a way to make a bacterium into a monkey, which differ in respect to thousands if not millions of different genes that must be coordinated; it is on the other hand a possible way in which a single gene from a higher organism, like a mouse, a monkey or even a man, could be implanted into a bacterium in order to learn more about how it works in a standardized setting. This would be similar to removing a suspicious transistor from a complicated computer and testing it in a smaller and well calibrated diagnostic test machine. The perfection of these procedures then opens up the possibility of diagnosing genetic variability in man by extracting individual genes in question and testing them in a bacterial context; probably even more important, it can be expected to give immense new insight into the way in which individual human genes function. Further on down the road we can visualize the extension of these procedures to provide a basis for producing important human hormones and other products by fermentation processes like those now used for the

production of important antibiotics. The idea would be to obtain the DNA from human cells which is essential for producing specific proteins like insulin or like the human growth hormone or like many other potentially important therapeutic products, and implanting these genes into bacteria to provide strains for the medical production processes just mentioned. In fact, this approach should lead to the discovery of human proteins of whose existence and importance we are now unaware, or which are too difficult to investigate because they are produced in too small amounts.

A second line of investigation more immediately concerns biochemical studies on human beings. Fortunately, we are able to avoid many rather serious ethical and technical problems that would be involved in serious intrusions into the human body. Instead, we can concentrate our efforts on the study of the biochemistry of urine which is, of course, the waste-bag of human metabolism and contains in it innumerable clues to variations in biochemical processes within the body. Of course, a great deal of clinical chemistry today is already done on urine but this is for the most part devoted to studies on a few well understood compounds for which analytical procedures were devised long ago. An example in point is the detection of sugar in urine as a means for the diagnosis of diabetes, a process which can now be done even in a home-kit.

The important innovation in our work in this field is the application of highly advanced and sophisticated new analytical methods which are a by-product of space-research which our laboratories had been involved in for some years before. In order to assist the NASA in its program of studying the possibility of life on other planets, we have helped to design the kinds of experimental instrumentation that are intended to be used on the Mars-probes and on other missions. In order to satisfy the requirements of space research, these instruments had to be highly sensitive and capable of being run automatically, so as to deliver information without attendance and on a very large scale.

For the past two years we have been turning our attention to the use of these analytical devices for problems in human clinical genetics. The principal arena of instrumentation concerns devices called the mass spectrometer and the gas chromatograph. We have put particular emphasis into managing the operation of these instruments under the control of a computer and this has become a field in which we have developed particular experience and expertise.

The test populations whose urine is used for these studies consist initially of newborn babies from the Stanford clinics, especially those who show signs of medical problems that are obscure and poorly understood. Already we know that in many cases the urine from these babies can be helpful in understanding their medical problems and will be a key to the discovery of new forms of genetic defect besides those that have already been listed. The newborns are particularly appropriate for this kind of investigation because they are already under very careful medical scrutiny in order to serve their particular health needs, and because they have an obviously well controlled diet. It is already known that dietary variations can have an important influence on urinary output which at this stage of our study would confuse our results.

The virtue of the GC-MS approach is that, as has already been shown, many thousands of different compounds can be recognized in a single urine and their precise structure determined by the use of the mass spectrometer. We have also learned how to automate this process to a very considerable degree so that the computer does a great deal of the very difficult and tedious work that would be involved in keeping track of so different compounds. These methods are also extremely sensitive, so that minute amounts of material can be readily detected. For example, with some children we find the complication that mysterious compounds have appeared in the urine when some medicinal salve had been rubbed on a skin rash!

In addition to the studies on the astronauts we have also arranged with the space agency to be involved cooperatively in using thee techniques for the surveillance of the health of astronauts on prolonged missions. Eventually when we have obtained a sufficient backlog of information on normal and diseased individuals under highly standardized conditions we will then also be able to study the urine of people whose diet is under less rigorous control and this will enable a considerable enlargement of the scope of these investigations.

The very broad range of chemical materials that these methods can identify, and the very high sensitivity of these procedures, make it possible to detect abberations of metabolism that might readily be overlooked by other methods and several examples have already been of practical significance. Trace-amounts of new materials may be expected to be quite important in learning more of the biochemical basis of mental disease and of other forms of handicap which are now only very poorly understood.

On a smaller scale we are also studying other body fluids to determine their utility for screening for genetic variations. Since other workers have been able to show that drugs can be detected even in human breath by these kinds of procedures, these should be promising extensions of this approach, appropriate for large-scale screening with a minimum of personal intrusion. As these methods are developed further, it will of course be important to design long-term experiments in the course of which many individuals will have the opportunity of being followed up from birth onwards, so as to understand the full significance of the variations that are detected in the newborn state. Needless to say, these programs are practically and ethically possible only with the full understanding and cooperation of the participating subject.

There is one other arena of investigation that deserves mention here -- the study of chemicals which can induce genetic damage which is the ultimate

culprit for genetic defect. Chemical changes in the genes, so called gene mutations, are of course an indispensable part of our evolutionary legacy. Without them, subject to the filtering of natural selection, the human species could never have evolved. But in the process we also accumulate many deleterious mutations. Today, in an environment to which modern industrial society now makes an important additional contribution, we face the risk of adding to our burden of genetic heritage by new mutations damaging the germ line. Although the general importance of this problem of genetic hygiene has been widely discussed, we have all too little specific information with which to design sensible social policy. There has been a great deal of controversy about the possible hazards of nuclear power and other sources of radiation to the stability of our genes but this controversy is noted more for its heat than for the quantitative information that we should have in order to make sensible decisions. Much the same can be said for a large number of chemicals which are potential threats of equal importance.

We have been undertaking some studies particularly on the potential genetic hazards of chlorine because this compound has been surprisingly little studied in spite of its very wide and important use in the sanitation of water supplies. In the test tube chlorine does indeed react with DNA, the genetic material, but our further studies have indicated that as such it is probably a negligible hazard in ordinary use. However, the studies are by no means complete; and furthermore, we have good reason to believe that there are certain complexes of chlorine with other organic materials that may well occur in water supplies that may present a more serious hazard. Surprisingly we have had great difficulty in getting funding for this particular line of research, perhaps owing to an exaggerated sense of conservatism on the part of public health authorities who may view the asking of such questions as being rather embarassing for their efforts at using chlorine for water sanitation. We have been quite careful

to avoid arousing public hysteria about an issue of this kind but nevertheless feel rather deeply that it badly needs to be scientifically investigated. These studies are best done initially with microorganisms for the reasons indicated above and then promising findings can be translated to studies with experimental animals and with human subjects. For example, we have not undertaken, but intend to in due course, a study to determine whether people who drink chlorinated water supplies are excreting a different set of chemical compounds in their urine from those who confine themselves to unchlorinated water. Because of the minute amounts of chlorine,or comparable substances in other experiments, that are involved in these studies we would have no hope of being able to detect metabolic changes except for the extraordinarily high sensitivity and precision of the analytical techniques that were mentioned previously.

These are long-range projects of the Genetics Department. With the exception of the chlorine mutagenesis program, they have enjoyed support from time to time from government sources but never to the extent that would enable us to make the maximum contribution to basic science and public health that these new methods and ideas open up. In addition, during the current era there have been the most distressing convulsions in patterns of federal support for health research that will not prevent us from continuing these efforts but have been severely disruptive for long-range planning, for the recruitment of skilled personnel, and have diverted a great deal of time that the principal investigator could more profitably apply to the scientific issues.